REMARKS

Following entry of this amendment, claims 19 to 41 and 44 to 56 are pending in the application. Claims 19 to 24, 29, and 30 are currently under consideration. Applicants have amended claim 19 and claim 30. Support for the amendment to claim 19 can be found in the specification, *e.g.*, at page 10, lines 5-17. Claim 30 has been amended to depend from claim 29 rather than claim 19. Applicants have cancelled claims 42 and 43 without prejudice or disclaimer. No new matter is added with these amendments.

Rejection of Claims 24, 42, and 43 under 35 U.S.C. § 112, First Paragraph

The Examiner rejected claims 24, 42, and 43 under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled. Action at page 2. The Examiner stated that "[t]he specification teaches apoptosis induced in cell culture by mAb74 (produced by hybridoma ATCC No. HB 12078), wherein the induction of apoptosis was an unexpected result (p. 4, lines 25-28)." *Id.* at page 4. The Examiner alleged, however, that

> [o]ne cannot extrapolate the disclosure of the specification to the scope of the claims because the specification does not provide examples or guidance for treating cancer in a patient comprising administering a monoclonal antibody produced by hybridoma cell line ATCC No. HB 12078, or an antibody that binds to the same epitope, wherein the antibody induces apoptosis.

Action at page 4.

The Examiner also alleged that "[t]he specification discloses that mAb74 (produced by hybridoma ATCC No. HB 12078) induced apoptosis in cell lines overexpressing Her2, however, one skilled in the art would not extrapolate the induction

of apoptosis in cell culture to the treatment of cancer in a patient because of the lack of physiological, immunological, environmental properties present during *in vitro* testing." *Id.* Finally, the Examiner alleged that "one of skill in the art would be forced into undue experimentation to practice the claimed invention." *Id.* at page 7.

Applicants respectfully traverse. Claim 24 recites "[t]he method of claim 19, wherein the antibody or fragment thereof is produced by the hybridoma cell line ATCC No. HB 12078." Claim 19 has been amended to incorporate an element from claim 42, and now recites "[a] method for treating cancer characterized by overexpression of Her2, in a patient, comprising administering an antibody or fragment thereof that binds an epitope on Her2 which is recognized by a monoclonal antibody produced by hybridoma cell line ATCC. No. HB 12078, and which induces apoptosis in Her2 overexpressing cells." Rejected claims 42 and 43 have been cancelled without prejudice or disclaimer because they are now duplicative of claims 29 and 30, which recite "[t]he method of claim 19, wherein the antibody or fragment thereof is administered with a chemotherapeutic agent" and "[t]he method of claim 29, wherein the chemotherapeutic agent is selected from cisplatin and 5-fluorouracil," respectively. Applicants will therefore address the rejection with respect to claims 19, 24, 29, and 30.

Applicants assert that the teachings in the specification and the general knowledge in the art concerning administering antibodies to treat conditions in patients enable claims 19, 24, 29, and 30. Applicants assert that the specification teaches how to make an antibody or fragment thereof that binds to Her2, *e.g.*, at Example 2. The specification also teaches how to select an antibody that induces apoptosis in Her2 overexpressing cells, *e.g.*, at Example 6. In addition, the specification teaches how to make pharmaceutical compositions comprising an antibody or fragment thereof that

binds Her2 and induces apoptosis in Her2 overexpressing cells, *e.g.*, at page 12, lines 3 to 14. The specification also teaches certain routes of administration for such pharmaceutical compositions, *e.g.* at page 11, lines 29 to 33.

In addition, following *In re Wands*, screening hybridomas to identify an antibody with the desired characteristics is routine, not undue experimentation. *In re Wands*, 858 F.2d 731, 737, and 740 (Fed. Cir. 1988). One must therefore conclude that it is not undue experimentation for one skilled in the art to make antibodies to Her2 and select those with desired characteristics, *i.e.*, antibodies that bind to Her2 and induce apoptosis in Her2 overexpressing cells. Thus, the antibodies recited in the present claims are adequately enabled by the specification and the knowledge in the art.

To provide evidence that certain claims were enabled, Applicants submitted the English abstract of Sasaki et al., "Monoclonal antibody induces apoptosis against cancer cells," *Nippon Rinsho* 60: 451-456 (2002), with the Response filed August 21, 2006. The Examiner, however, alleged that "there is insufficient evidentiary support from the English abstract to enable extrapolation of the *in vitro* results for a monoclonal antibody produced by hybridoma cell line ATCC No. HB 12078, or an antibody that binds to the same epitope, to the *in vivo* treatment of cancer." Action at page 15. The Examiner also alleged that the English abstract from Sasaki "does not enable the claimed invention, nor provide support for extrapolating in vitro assays to the treatment of cancer." Action at page 16.

Without acquiescing to the Examiner's contentions concerning Sasaki, Applicants provide Hinoda et al., "Monoclonal antibodies as effective therapeutic agents for solid tumors," *Cancer Sci.* 95(8):621-625 (2004), as additional evidence that the present claims are enabled. Although Hinoda was published after the filing date of the instant

application, its disclosure supports Applicants' assertion that the present claims are enabled because Hinoda teaches an antibody that induces apoptosis in Her2-expressing cells, and that has been shown to successfully treat cancer *in vivo*. *See, e.g.*, Hinoda at Abstract.

Specifically, Hinoda shows a mouse-human chimeric anti-Her2 antibody, CH401, that induces apoptosis in Her2 overexpressing cells *in vitro*. *See, e.g.,* Hinoda at page 621, right column, and page 622, left column and Figure 2. In fact, "[t]he in vitro cytolytic activity of CH401 was demonstrated in all the HER2-expressing human cultured cell lines tested (Fig. 2)." *Id.* at page 622, left column. Hinoda also demonstrates that CH401 induces apoptosis *in vivo*. *See, e.g., id.* at page 622, Figure 3. Thus, Hinoda teaches a Her2-binding antibody that induces apoptosis *in vitro* and, as one skilled in the art would expect, also retains that apoptotic activity *in vivo*. In addition, Hinoda shows the use of CH401 in the treatment of cancer. *See, e.g., id.* at page 622, Figure 1. As shown in Figure 1, treatment with CH401 suppressed tumor growth in SCID mice, while treatment with a control antibody failed to suppress tumor growth. *See id.*

In sum, Hinoda teaches a Her2-binding antibody that (1) induces apoptosis *in vitro*, (2) retains its apoptotic activity in vivo, and (3) is effective in treating cancer. Applicants therefore assert that Hinoda supports the conclusion that even though the anti-Her2 antibodies recited in the present claims have an unexpected property, *i.e.* induction of apoptosis in Her2-overexpressing cells, that property does not adversely affect the ability of one skilled in the art to use the antibodies in the claimed methods according to the teachings of the specification and the knowledge in the art.

Feldman, Weiner, and Maini

Applicants submitted Feldman, Weiner, and Maini with the Response After Final, filed August 21, 2006, as support for Applicants' assertion that certain methods of administering antibodies to patients with diseases were known in the art prior to the filing date of the present application. The Examiner alleged that Feldman, Weiner, and Maini "do not teach or enable the treatment of Her2 overexpressing cancer in a patient comprising administering a monoclonal antibody produced by hybridoma cell line ATCC No. HB 12078, or an antibody that binds to the same epitope, wherein the antibody induces apoptosis." Action at page 14. The Examiner also noted that these articles are "not related to Her2, cancer, or her2 antibodies." *Id.* at pages 14 and 15.

Applicants respectfully traverse. Although Feldman, Weiner, and Maini do not use Her2-binding antibodies, the teachings of Feldman, Weiner, and Maini are relevant to the enablement of the present claims because they demonstrate that it was within the skill in the art at the time of filing to administer antibodies to treat conditions in patients. Applicants remind the Examiner that the standard for enablement is whether one skilled in the art could practice the claimed invention using the teaching of the specification *and information known in the art* without undue experimentation. *See, e.g.,* MPEP § 2164; *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Thus, the enablement standard permits one skilled in the art to use not just the specification, but also the relevant knowledge and skills in the art, in order to practice the claimed invention. Furthermore, "one skilled in the art" is just that - a person *having skill* in the art, not an automaton. Applicants assert that one skilled in the art would certainly consider documents showing treatment of various conditions using antibodies to be relevant to practicing a method involving treatment of cancer using antibodies, and would be able to apply those

documents, and the specification and other documents and knowledge in the art, to practice the claimed methods.

The Examiner appears to require that Applicants produce an anticipating reference showing precisely the claimed invention in order to demonstrate enablement of the present claims. Such a requirement is not only nonsensical, it is contrary to the standard set forth in the MPEP, which explicitly states that "[t]he evidence provided by applicant **need not be conclusive** but merely convincing to one skilled in the art." MPEP § 2164.05 (underlining in original, bolding added). Applicants assert, therefore, that the Examiner cannot simply dismiss Feldman, Weiner, and Maini as allegedly being "not related to Her2, cancer, or her2 antibodies" without explaining why *one skilled in the art* would not find their teachings relevant to the enablement of the claimed method.[1]

Applicants assert that one skilled in the art, using the teaching of the specification and the knowledge in the art, as exemplified by Feldman, Weiner, and Maini, could practice the claimed method without undue experimentation. Moreover, Applicants assert that Hinoda strongly supports Applicants' assertion that the present claims are enabled.

In re Brana

The Examiner attempts to rely on *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995), to "demonstrate[ ] requirements for enablement of a product for pharmaceutical use *in vivo*." Action at page 6. The Examiner contended that

[1] Furthermore, contrary to the Examiner's contention that those documents are not related to cancer, Applicants point out that Weiner describes the use of an antibody in Phase I clinical trials to treat patients with end stage CD19+ leukemia/lymphoma. *See* Weiner at page 204. Applicants maintain, however, that all three documents are relevant to the enablement of the present claims.

> [p]ost-filing art teaching the claimed antibody treating cancer *in vivo* would be enabling for *in vivo* treatment. Or as stated in the enablement rejection of section 5 with regards to *In re Brana*, prior art disclosing an[d] antibody that binds to the same epitope **or shares the same structure and function** and is enabled for treating cancer would enable the claimed antibody for treating cancer.

Action at page 14. The Examiner alleged, however, that "neither the prior art nor post-filing art enable the claimed antibodies for treating cancer." *Id.* The Examiner also alleged that

> [i]n the instant application, unlike in *In re Brana*, the antibody that binds to Her2 has an "unexpected" result of inducing apoptosis in vitro, and a search of the current art does not teach or enable a monoclonal antibody produced by hybridoma cell line ATCC No. HB 12078, or an antibody that binds to the same epitope to treat cancer in a patient.

Id. at page 6.

Applicants respectfully traverse. Applicants assert that the agent used to treat cancer discussed in Hinoda is structurally and functionally similar to the agent used to treat cancer recited in the present claims. Both agents are antibodies, which share a common structure. In addition, both agents demonstrate similar functions: they both bind to the same antigen, Her2, and they both induce apoptosis in Her2-expressing cells. Furthermore, Hinoda demonstrates that CH401, which is structurally and functionally similar to the antibody recited in the present claims, is effective at treating cancer *in vivo*. Thus, Applicants assert that, following *In re Brana*, Hinoda strongly supports the enablement of the present claims.

The Examiner, however, appears to require that the post filing art disclose the *exact* method recited in the present claims, by requiring applicant to provide a document showing not just a structurally and functionally similar antibody, but an antibody that is encompassed by the present claims. The Examiner is therefore requiring conclusive

evidence of enablement, which directly contradicts the standard set forth in the MPEP. *See* MPEP § 2164.05 ("The evidence provided by applicant need not be conclusive but merely convincing to one skilled in the art."). Applicants assert that they have provided ample convincing evidence to support the enablement of the present claims, which is all that is required.

Further, Applicants reiterate that even if it is "surprising" or "unexpected" that an antibody that binds Her2 could induce apoptosis in Her2-overexpressing cells, any alleged unpredictability with respect to that property is not relevant to the question of whether one skilled in the art could have used an antibody that has already been selected to have that property in a method for treating cancer. In other words, once the antibody with the property has been selected, it is not surprising or unexpected that it would retain that property in a method for treating cancer. In fact, one skilled in the art would expect the antibody to continue to have that property *in vivo*. Moreover, Hinoda strongly supports that conclusion.

In Vitro Models for Cancer Treatment

The Examiner continued to alleged that

> [t]hose of skill in the art recognize that *in vitro* assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in vitro* assay does not permit a single extrapolation of *in vitro* assays to human diagnostic efficacy with any reasonable degree of predictability.

Action at page 4. In addition, the Examiner alleged that "the *in vitro* model used in the specification is not recognized as correlating to the *in vivo* treatment of cancer and is

not accepted as reasonably correlating for the reasons set forth above and in the enablement rejection of section 5 with regards to *in vitro* models." *Id.* at page 18.

Applicants respectfully traverse. Applicants assert that evidence of record most relevant to enablement of the claimed method, for example, Voskoglou-Nomikos, teaches that the particular cell lines used in the *in vitro* experiments described in the specification are good predictors of in vivo activity. The Examiner ignores that evidence in favor of much less relevant documents that discuss either completely unrelated cell lines or broad generalizations about cell lines as a whole.

Applicants point to the MPEP section pertaining to *in vitro* / *in vivo* correlation, which states that

> the issue of "correlation" is also dependent on the state of the prior art. In other words, **if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate.** Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether **one skilled in the art would accept the model as reasonably correlating** to the condition.

MPEP § 2164.02 (citing *In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995) (emphasis added)). Applicants note that the MPEP states that the Examiner must accept the model as correlating unless the Examiner has evidence that *the model* does not correlate. That is, the Examiner must present evidence that the particular model at issue, the NCI Panel, is not predictive of *in vivo* results, not merely that some unrelated cell lines are not predictive. Moreover, the Examiner must consider the evidence from the standpoint of one skilled in the art, who Applicants assert would consider Voskoglou-Nomikos to be most relevant and strongly supportive of the predictive value of the cell lines on the NCI Panel. Applicants further assert that one skilled in the art,

presented with Voskoglou-Nomikos and the Examiner's documents dealing with unrelated cell lines and broad generalizations, would *still* consider Voskoglou-Nomikos to be strong evidence of the existence of a correlation between *in vitro* results using the NCI Panel cell lines and *in vivo* efficacy. The Examiner has not explained why she believes that one skilled in the art would disregard the most relevant evidence, which directly addresses the cell lines used in the specification, in favor of documents that discuss unrelated cell lines and make broad generalizations.

Applicants will now address the Examiner's contentions with respect to each document.

Voskoglou-Nomikos

The Examiner alleged that Voskoglou-Nomikos "teach[es] clinical predictive value of the *in vitro* cell line for compounds or chemicals and does not teach the predictive value of cell culture studies for Her2 antibodies and treatment of Her2 overexpressing cancer." Action at page 17. The Examiner alleged that the teachings of Voskoglou-Nomikos "do[] not enable the extrapolation of *in vitro* data to the enablement of treating cancer comprising administering a monoclonal antibody produced by hybridoma cell line ATCC No. HB 12078, or an antibody that binds to the same epitope." *Id.* The Examiner further alleged that the claimed invention is not "related to compounds in the context of [Voskoglou-Nomikos]." *Id.*

Applicants respectfully traverse. Applicants assert that the Examiner has again failed to refute the repeated assertions in Voskoglou-Nomikos that the NCI Panel is not only a good predictor of Phase II clinical trial results, but is a better predictor than mouse models or even human xenograph models. Applicants also assert that the

Examiner has again failed to provide any evidence demonstrating that the NCI panel, specifically, is not a reasonable predictor of *in vivo* results.

The Examiner again appears to require that applicant provide an anticipating reference and/or conclusive evidence that employs the claimed antibodies in order to support the enablement of the present claims. The Examiner also appears to require that each piece of evidence, taken on its own, enable every element of the claims. The MPEP clearly states that the Examiner must consider the evidence *as a whole*, not piece by piece. See MPEP § 2164.05 ("Determination of Enablement Based on Evidence as a Whole"). Applicants assert that, viewed as a whole, the evidence thus far submitted would be convincing to one skilled in the art that the present claims are enabled. For example, Voskoglou-Nomikos may not explicitly discuss "treating cancer comprising administering a monoclonal antibody produced by hybridoma cell line ATCC No. HB 12078," but Applicants assert that one skilled in the art would consider Voskoglou-Nomikos to be relevant to the question of whether the *in vitro* data presented in the specification correlates to *in vivo* efficacy of the antibodies recited in the claims. One skilled in the art would view Voskoglou-Nomikos as relevant evidence supporting Applicants' assertion that such a correlation exists. Thus, considering Voskoglou-Nomikos along with, for example, Feldman, Weiner, and Maini, which teach treatment of certain conditions using antibodies, and Hinoda, which shows that a Her2 antibody that induces apoptosis *in vitro* has been successfully used to treat cancer *in vivo*, provides convincing evidence of enablement of the present claims.

Finally, it is unclear why the Examiner has stated that the claimed invention is not related to compounds in the context of Voskoglou-Nomikos. Applicants point out that Voskoglou-Nomikos does not offer any definition of the term "compound." Instead, the

author appears to interchangeably use the terms "drug," "agent," "compound," and "therapeutic." *See* the entire article. Applicants assert that one skilled in the art would consider an antibody used to treat cancer as a "drug," "agent," "compound," and/or "therapeutic." Furthermore, Table 2 of Voskoglou-Nomikos shows the "[m]echanisms of action of drugs used in clinical vs. pre-clinical correlations for the in vitro cell line model (Fig. 1)." Voskoglou-Nomikos at page 4233. Applicants note that at least two of the compounds in Table 2, taxol and taxotere, induce apoptosis. Thus, at least two of the compounds used in Voskoglou-Nomikos to demonstrate the good correlation between *in vitro* results using the NCI Panel and *in vivo* efficacy have a similar mechanism of action as the antibodies recited in the present claims.

Freshney

The Examiner alleged that Freshney teaches that "it is well recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*." Action at page 5. Specifically, the Examiner alleged

> [t]hese differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks in the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant in vitro but may not be truly representative of the tissue from which the cells were derived.

Id. The Examiner alleged that "[t]his has often led to tissue culture being regarded in a rather skeptical light." *Id.*

Applicants respectfully traverse. The issue is not whether certain cell lines are identical to an *in vivo* environment but whether one of skill in the art could practice the claims without undue experimentation. As part of that inquiry, Applicants assert that one skilled in the art would accept the *in vitro* data presented in the specification as

reasonably correlating to *in vivo* efficacy. Even though Freshney fails to discuss the NCI Panel directly, Freshney still recognizes the predictive value of cell lines, stating that

> [a]nimal models have always played an important role in both contexts, and although **cell culture systems have figured largely in the field of cancer chemotherapy, where the potential value of such systems for cytotoxicity and viability testing is now widely accepted**, there is increasing pressure for a more comprehensive adoption of in vitro testing in both spheres of application.

Freshney at page 183, first full paragraph (emphasis added). Thus, Freshney supports Applicants' assertion that one skilled in the art, viewing the evidence *as a whole*, which includes Voskoglou-Nomikos, would conclude that there exists a reasonable correlation between *in vitro* results using certain cell lines and *in vivo* results. As discussed above, Voskoglou-Nomikos teaches that the NCI Panel not only is a good predictor of Phase II clinical trial results, but is a better predictor than mouse models or even human xenograph models. Voskoglou-Nomikos at 4235-36. Applicants assert that one skilled in the art would view Freshney, which teaches that cell culture systems are now widely accepted, as supporting the teachings of Voskoglou-Nomikos.

Dermer

The Examiner alleged that Dermer teaches that "'petri dish cancer' is a poor representation of malignancy, with characteristics profoundly different from the human disease." Action at page 5. The Examiner also reiterates the allegation that "the concepts taught by Dermer are applicable to the NCI panel cell lines." *Id.* at page 19.

Applicants respectfully traverse. Applicants again point out that Dermer only discusses 3T3 cells, which are not part of the NCI Panel. The Examiner uses a document that makes broad generalizations about a single irrelevant cell line to refute

the much more relevant teachings of Voskoglou-Nomikos. Applicants again assert that one skilled in the art, properly considering the evidence *as a whole*, would conclude that Voskoglou-Nomikos is convincing evidence of the correlation between the *in vitro* data presented in the specification and *in vivo* efficacy of the antibodies recited in the claims, even in view of Dermer's statements about 3T3 cells. In fact, Dermer proposes using "models that mimic the human body and the developmental pathways of human cells, both normal and malignant." Applicants assert that the NCI Panel represents such a model.

Drexler

The Examiner alleged that Drexler teaches that "in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded." Action at page 6. The Examiner further alleged that Drexler teaches that "only a few cell lines containing cells that resemble the in vivo cancer cells have been established and even for the bona fide cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see abstract)." *Id.* Attempting to support the contention that Drexler applies to the NCI Panel, the Examiner alleged that "Drexler's concepts apply to other *in vitro* cell lines as even the NCI panel line, MDA-MB-435, may not have originated from breast cells." *Id.*

Applicants respectfully traverse. Applicants assert that Drexler's observations are specific to Hodgkin and Reed-Sternberg cells lines (H-RS cells) and are not generally applicable to the particular cell lines used in the present application. Applicants note that the Examiner has misquoted Drexler in a way that implies that

Drexler made broad generalizations about all cancer cell lines. The direct quote from Drexler specifically discusses Hodgkin and Reed-Sternberg cells:

> Only a few cell lines containing cells **that resemble in-vivo H-RS cells** have been established. Because the in-vitro culture conditions favor the self-propagation of residual normal cells, e.g., Epstein-Barr virus transformed B-lymphoblastoid cells or monocyte/macrophage monolayers, early attempts at culturing HD [Hodgkin's disease] tissue resulted mainly in the generation of such cell lines. Even for the bona fide HD cell lines it is difficult to prove that the immortalized cells originated from an H-RS cell.

Drexler at abstract (emphasis added). Thus, Drexler discusses a particular issue that exists with Hodgkin and Reed-Sternberg cells, and does not generalize those conclusions to any other cell lines.

Applicants assert that it is improper for the Examiner to generalize the results of Drexler to all cancer cell lines when even Drexler itself fails to do so. None of the cell lines discussed in Drexler is on the NCI Panel, nor does Drexler draw any conclusions concerning the NCI Panel from observations concerning H-RS cells. Drexler, in fact, states that "[d]evelopment of HD cell lines has proven to be rather difficult when compared with the results on leukemia and Non-Hodgkin lymphoma cells." *Id.* The Examiner must consider Drexler from the viewpoint of one skilled in the art, who would consider the conclusions of Drexler to be limited to Hodgkin and Reed-Sternberg cells, and not to all cell lines generally, as the Examiner contends. Applicants again assert that one skilled in the art, viewing the evidence *as a whole*, would consider Voskoglou-Nomikos to be most relevant to the issue of a correlation between *in vitro* data and *in vivo* efficacy.

Further, Applicants again assert that it is not relevant to the present claims, which recite a method for treating cancer, that MDA-MB-435 may be a melanoma cancer cell line rather than a breast cancer cell line. Simply because both MDA-MB-435 cells and

H-RS cell lines may happen to have disputed origins does not expand the scope of Drexler's observations beyond Hodgkin and Reed-Sternberg cells.

Applicants assert that the specification and the knowledge in the art enable one skilled in the art to practice the claimed invention without undue experimentation. When properly viewed as a whole from the standpoint of one skilled in the art, Applicants' evidence strongly supports the enablement of the present claims. This evidence includes Voskoglou-Nomikos, which teaches the correlation between the *in vitro* results using the cell lines discussed in the specification and the *in vivo* efficacy of the antibodies recited in the claims; Feldman, Weiner, and Maini, which teach treatment of certain conditions using antibodies; and Hinoda, which shows that a Her2 antibody that induces apoptosis *in vitro* has been successfully used to treat cancer *in vivo.*

Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 19-21, 29, and 30 under 35 U.S.C. § 102(b)

The Examiner rejected claims 19 to 21, 29, and 30 under 35 U.S.C. § 102(b), as allegedly being anticipated by Shepard et al., *J. of Clinical Immunology*, (1991) 11:117-127 (Shepard). *See* Action at page 8. The Examiner alleged that Shepard teaches "a method for treating cancer characterized by overexpression of Her2 comprising administering monoclonal antibody 4D5 that binds to Her2." *Id.* at page 9. The Examiner then cited Le et al., *Clinical Cancer Research*, (2000) 6:260-270, and alleged that "4D5 is known to induce apoptosis." *Id.*

Applicants respectfully traverse. In order to anticipate a claim, a document must teach "each and every element as set forth in the claim." MPEP § 2131. Solely to

expedite prosecution, and without acquiescing to the rejection, claim 19 has been amended to recite:

> 19. A method for treating cancer characterized by overexpression of Her2, in a patient, comprising administering an antibody or fragment thereof that binds an epitope on Her2 which is recognized by a monoclonal antibody produced by hybridoma cell line ATCC No. 12078, and which induces apoptosis in Her2 overexpressing cells.

Applicants assert that Shepard fails to teach "an antibody or fragment thereof that binds an epitope on Her2 which is recognized by a monoclonal antibody produced by hybridoma cell line ATCC No. 12078." Therefore, Shepard fails to anticipate claim 19. Claims 20, 21, 29, and 30 ultimately depend from claim 19, and are therefore not anticipated for at least the same reason. Applicants need not and do not address the Examiner's contentions with respect to Shepard and Le and certain elements of certain claims. By not addressing those contentions, Applicants in no way acquiesce to them.

Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b).

Rejection of Claims 23 and 22 under 35 U.S.C. § 103(a)

Claim 23

The Examiner rejected claim 23 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Shepard in view of U.S. Patent No. 5,001,225 (the '225 patent). Action at page 10. The Examiner acknowledged that "Shepard et al. does not teach that the Her2 antibody, monoclonal antibody 4D5, is a fragment," but alleged that the '225 patent teaches that:

> Fab and $F(ab')_2$ fragments lack the Fc fragment of an antibody, clear more rapidly from circulation and have less nonspecific tissue binding than intact antibody (col 9, lines

> 22-25) and further teach[es] that Fab, $F(ab')_2$ fragments may be used as well as the intact antibody in methods of treatments (col 9, lines 26-32).

Id.

Applicants respectfully traverse. Claim 23 depends from claim 19. As discussed above, Shepard fails to teach every element of claim 19. Further, Applicants assert that there would have been no suggestion to modify Shepard to arrive at the method of claim 19. Applicants assert that the '225 patent fails to remedy the deficiencies of Shepard. Applicants need not and do not address the Examiner's contentions concerning Shepard and the '225 patent and certain elements of claim 23. By not addressing these contentions, Applicants in no way acquiesce to those contentions.

Applicants respectfully request reconsideration and withdrawal of the rejection of claim 23 under 35 U.S.C. § 103(a) over Shepard in view of the '225 patent.

Claim 22

The Examiner rejected claim 22 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Shepard in view of Reichmann et al. (Nature, 1988, 332:323-327). Action at page 11. The Examiner alleged that Reichmann teaches that "murine monoclonal antibodies comprise foreign immunoglobulin that can elicit an anti-globulin response which may interfere with therapy or cause allergic or immune complex hypersensitivity." *Id.*

Applicants respectfully traverse. Claim 22 depends from claim 19. As discussed above, Shepard fails to teach every element of claim 19. Further, Applicants assert that there would have been no suggestion to modify Shepard to arrive at the method of claim 19. Applicants assert that Reichmann fails to remedy the deficiencies of Shepard. Applicants need not and do not address the Examiner's contentions concerning

Shepard and Reichmann and certain elements of claim 22. By not addressing these contentions, Applicants in no way acquiesce to those contentions.

Applicants respectfully request reconsideration and withdrawal of the rejection of claim 22 under 35 U.S.C. § 103(a) over Shepard in view of Reichmann.

Conclusion

Applicants assert that the application is in condition for allowance and respectfully request that the Examiner issue a timely Notice of Allowance. If the Examiner does not consider the present application to be allowable, the undersigned requests that, prior to taking action, the Examiner call her at (650) 849-6611 to set up an interview.

Please grant any extensions of time required to enter this Response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: July 25, 2007

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